

**REMARKS**

**I. Claim Status and Support for the Claim Amendments**

Claims 4-16 are all the claims pending in the application. The limitations of claim 5 have been incorporated into claim 4 and claim 5 has been cancelled. Additional claim amendments have been made to claims 6-15.

**II. The Claim Rejections under 35 U.S.C. § 112, second paragraph, are Moot**

The Office Action of 31 January 2007 rejected claims 4-16 under 35 U.S.C. § 112, second paragraph, as allegedly “being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.” To better capture the envisioned commercial embodiments, Applicants have amended claims 4-15. Applicants assert that the amendments to the claims render moot the outstanding indefiniteness rejections. Applicants request reconsideration and withdrawal of the indefiniteness rejection of claims 4-15. In addition, claim 16 was rejected because the word “highly” was allegedly confusing. Applicants point out, however, that claim 16 does not contain the word “highly.” Applicants request that the Office reconsider and withdraw the indefiniteness rejection of claim 16, as the rejection appears to be a typographical error.

**III. The Written Description Rejection under 35 U.S.C. § 112, first paragraph, is Traversed**

The Office Action of 31 January 2007 rejected claims 4-13 under 35 U.S.C. § 112, first paragraph, as allegedly “containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention.” Office Action of 31 January 2007, page XXX. Applicants respectfully disagree and assert that the specification fully describes the enabling for the claimed invention in view of the following remarks.

Specifically, the Office Action alleges that the specification “neither teaches the structures of all genes nor teaches how all *E. coli* strains will be modified. Therefore, one skilled

in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.” Office Action of 31 January 2007, page XXX. Applicants respectfully disagree and point out that the current invention is not directed towards gene manipulation, and therefore the application need not describe the “structures of all genes” to show evidence of possession of the claimed invention. Rather, the present invention is directed towards strains of *E. coli* that express an exogenous gene. The strains are defined by a phenotype rather than a genotype, *i.e.*, the strain is defined by a stress response that is measured by hydrogen peroxide decomposition activity. Thus, the application needs to only describe “selection strain[s that are] selected using hydrogen peroxide decomposition activity.” To that end, the application describes at least 24 strains that have a hydrogen peroxide decomposition index of greater than 1.0. *See Example 5 and table 4 of Pregrant Publication No. 2006/0234331.* Accordingly, Applicants contend that the application fully describes *E. coli* selection strains as claimed in the present invention. Further, the representative number of strains that display the claimed phenotype clearly would indicate to one of skill in the art that the inventors were in possession of the claimed invention at the time of filing the application.

#### **IV. The Enablement Rejection under 35 U.S.C. §112, first paragraph, is Traversed**

The Office Action of 31 January 2007 rejected claims 4-13 under 35 U.S.C. § 112, first paragraph, because the specification allegedly is not enabling. Specifically, the Office Action asserts that “[t]he specification fails to describe how any *E. coli* strain be modified to express any exogenous gene or any phenylalanine ammonia lyase gene.” Office Action of 31 January 2007, page 5. Applicants respectfully disagree and request reconsideration and withdrawal of the rejection.

Again, Applicants point out that the invention is directed to *E. coli* strains with a particular phenotype, rather than a specific genotype. Thus, the specification needs to enable strains that are identified by hydrogen peroxide decomposition. Applicants assert that the specification teaches one of skill in the art how to make and use at least 24 strains that are identified by their ability to decompose hydrogen peroxide. *See Example 5, Table 4.*

Moreover, the instant invention neither claims, nor does it require, a knowledge as to how to introduce and/or define genotypic mutations in *E. coli* that manifest as an increased hydrogen peroxide decomposition activity. Indeed, the specification clearly states that “during the selection of the mutant strain, it is not necessary in particular to conduct mutation treatment.” Consistent with this, the Applicants were able to isolate 24 independent clones from an *E. coli* XL1-Blue strain population exhibiting increased hydrogen peroxide decomposition activity, without the need for a mutagenesis step. Each and every independent clone (24/24) also exhibited an increase in expression level of a normally unstable exogenous gene. Thus, Since the specification fully describes to one skilled in the art a method for identifying and selecting an *E. coli* strain that exhibits increased expression of an unstable exogenous gene, using hydrogen peroxide decomposition activity as an index, the specification is thus fully enabling for one of skill in the art to practice the claimed invention. Accordingly, Applicants respectfully request that the remaining enablement rejections be withdrawn.

**V. Claim Rejections under 35 U.S.C. § 102(b) are Moot**

The Office Action of 31 January 2007 rejected claims 4 and 6 under 35 U.S.C. § 102(b), as allegedly “being anticipated by Hitagawa et al. (JP 08-140671).” To better capture the envisioned commercial embodiments, Applicants have amended claim 4 with the limitations of claim 5, which previously was not rejected under 35 U.S.C. § 102(b). Since the amendments to claim 4 flow through to its dependent claims, Applicants assert that the anticipation rejection of claim 6 is also moot. Accordingly, Applicants respectfully request reconsideration and withdrawal of the anticipation rejections.

**VI. Claim Rejections under 35 U.S.C. § 103(a)**

The Office Action rejects claims 4-15 as allegedly unpatentable over Lockwood et al. (WO 94/19472) and in view of Rowbury et al. (J. Appld. Microbiol. 2001, 90, 677-695) and Seaver et al. (J. Bacteriol. 2001. pp7182-7189). Applicants respectfully disagree that the claimed invention is obvious in view of the following remarks.

Specifically, the Office Action alleges that “[c]laims 4-15 are directed to *E. coli* strain which express exogenous gene encoding pal protein wherein said strain has high stress response factor and wherein said strain is selected by measuring hydrogen peroxide decomposition activity as a stress response factor.” Applicants respectfully disagree with this Office’s characterization of the present invention. As an initial matter, not all of claims 4-15 are directed to an “*E. coli* strain which express exogenous gene encoding pal protein wherein said strain has high stress response factor” as the Office Action alleges. Rather, only claims 9-11 specifically require the phenylalanine ammonia lyase (pal) protein.

To establish a *prima facie* case of obviousness, three criteria must be established. First, the references must teach each and every limitation of the currently claimed invention, *In re Royka*, 490 F.2d 981, 985 (C.C.P.A. 1974). Second, there must be some suggestion or motivation within the references themselves, or within the knowledge of one of ordinary skill in the art, to combine the references to arrive at the claimed invention. Finally, there must be a reasonable expectation of success in combining the references, and this expectation of success must also be found in the references as well. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991).

The Office Action alleges that Lockwood et al. “teach an *E. coli* strain that highly expresses genes encoding unstable proteins, such as the Pal protein.” Applicants respectfully disagree with this characterization of Lockwood and assert that Lockwood fails to teach expressing unstable proteins. Instead, Lockwood et al. at best, describe the generation of a shuttle vector containing an exogenous gene that may be transformed into either prokaryotic (*E. coli*) or eukaryotic (*Saccharomyces cerevisiae*) cells to express a protein of interest. Thus, Lockwood et al. fails to describe an *E. coli* strain, as the Office Action alleges. Thus, one skilled in the art wishing to express an unstable protein would take no guidance from Lockwood.

The Office Action alleges that Lockwood et al. “is silent about a correlation between stress response and high an expression of exogenous gene in *E. coli*” and that Rowbury et al. “teach that for cells of microorganisms, such as *E. coli* the stress response increases upon high expression of exogenous genes.” The Office Action then concludes that “it would have been obvious to a person of ordinary skill in the art to correlate high expression in *E. coli* strain of the

exogenous gene (encoding the unstable protein Pal) with the stress response as taught by Rowbury et al.” Applicants respectfully disagree and request that the Office clearly indicate which portion of Rowbury et al. supports the alleged teaching relied upon in the Office Action, since Applicants were unable to locate any such teaching within Rowbury et al. At no point does Rowbury et al. even suggest that a cellular stress response can be invoked by high expression of an exogenous gene. Accordingly, Applicants assert that the combination of Lockwood and Rowbury fails to teach one skilled in the art each and every element of the claimed invention.

Moreover, Seaver does not rectify the deficiencies of Lockwood and/or Rowbury. Indeed, the Office Action alleges that Seaver et al. “teach measurement of hydrogen peroxide decomposition activity in growing *E. coli* as a means of stress response factor.” Applicants respectfully disagree and request that the Office clearly indicate which portion of Seaver et al. supports the alleged teaching relied upon in the Office Action, since Applicants were unable to locate any such teaching within Seaver et al. In fact, Seaver et al. fails to teach or even suggest that the hydrogen decomposition activity can be used as an indicator of a high stress response. Accordingly, Applicants assert that Seaver et al. fails to “teach measurement of hydrogen peroxide decomposition activity in growing *E. coli* as a means of stress response factor.” Accordingly, the combination of Lockwood, Rowbury and Seaver fails to disclose each and every element of the claimed invention. The combination of Lockwood, Rowbury and Seaver, therefore, fails to establish a *prima facie* case of obviousness over the claimed invention.

Furthermore, Applicants assert that there is no suggestion or motivation to combine these teachings within the references themselves. There is no teaching to disclose that that hydrogen peroxide decomposition activity may be used as a measure of stress response, or that an increased stress response may correlate with high expression of an exogenous unstable protein. Applicants also assert that one of ordinary skill in the art would not be motivated to combine the references to arrive at the claimed invention, since the state of the art at the time the invention was conceived would have taught away from the claimed invention. Specifically, prior to the presently claimed invention, increased cellular stress in response to the expression of an exogenous gene would have been interpreted as a negative response to the exogenous gene and

one of skill in the art would have been motivated to suppress exogenous gene expression in an attempt to alleviate the increased stress. Considering the lack of motivation to combine these references, one skilled in the art would not possess an *a priori* expectation that combining these three references would somehow lead to the identification of *E. coli* selection strains.

Thus, because the combination of claimed references fails to teach each and every limitation of the claimed invention, and because there would be no motivation to combine the references with a reasonable expectation of success, the cited references fail to render obvious the claimed invention. Applicants respectfully request reconsideration and withdrawal of the remaining obviousness rejections.

**VI. Conclusion**

Applicants have amended claims 4 and 6-15, and have cancelled claim 5. Applicants assert that, although not indicated as such, claim 16 was previously allowable. In view of the claim amendments and arguments presented herein, Applicants request reconsideration and withdrawal of the outstanding rejections of claims 4-16.

Should the Examiner believe that further discussion of any remaining issues would advance the prosecution, he or she is invited to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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